APPLICATION OF BIOPHYSICAL RESEARCH TO MEDICAL PROBLEMS.

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The research, part of which is reported in this paper, is a further extension of previous studies undertaken for the purpose of ascertaining to what extent biophysical methods can be used in the investigation and interpretation of medical problems. Our observations of the effect of certain agencies such as adrenalin, anesthetics, stimulants, electrolytes; etc., on the temperature of various organs and tissues of the body have been made with the thought that if the effect of these influences should prove to be uniform and consistent with biological facts, these studies would lead to a wider use of biophysical methods. There are many other studies which will be reported in a later paper in which we expect to set forth an interpretation of our findings. At the present time we wish only to make known the facts which have appeared in these investigations.

Several similar attempts to study temperature changes in the tissues of animals under different conditions have been carried out in the past. In addition to the literature reported in a previous publication, we may especially mention the work of Mosso,[1] who measured the temperature changes by means of a very sensitive mercury thermometer. He believed that he had found a very great change in the metabolism of the brain followed the injections of certain drugs, among them being absinthe and strychnin. Hill and Nabarro,[2] however, criticized Mosso's work and made evident that his results were due mainly to the action of the drugs upon the blood circulation.

The amount of oxygen used in the metabolic processes in a state of rest and of excitation is known for many of the body organs in which excitation usually causes a several-fold increased consumption. How the energy corresponding to this oxygen consumption is used; how much is transformed into heat; and how much is used by the organ in the performance of its functions, are questions whose an-

[1] Mosso, *Proc. Roy. Soc.*, London, 1892.

[2] Hill, L. and Nabarro, D. N., *Jour. Physiol.*, 1895, XVIII., 218.

swers have not been directly determined for most organs. In the case of a muscle at work, A. V. Hill[3] has found that there is a maximum efficiency of fifty per cent. From an estimation of the work done by the organs it is safe to assume that for most organs the major portion of the chemical energy obtained through the oxygen consumption is directly transformed into heat. The chemical energy of the oxygen consumed by an organ under excitation corresponds to a temperature increase of a few tenths of a degree Centigrade per minute. The magnitude of this change indicates the feasibility of employing thermocouples for the temperature measurements in the study of metabolic processes.

In the studies reported here our attention has been directed especially to the measurement of the temperature changes which occur in the brain. As compared with most other organs, the oxygen consumption of the brain is large. It seems probable that the energy corresponding to this consumption is not directly converted into heat for the sole purpose of maintaining the brain temperature, but that it is primarily used by the brain in its special activities, finally appearing as heat in the brain or in other parts of the body. If this is so we would expect that activation of the brain would be accompanied by temperature changes large enough to be recorded.

It is evident, however, that changes in the circulation of the blood, due to vaso-constriction and vaso-dilation in the different parts of the body, must be an important factor in the production of the temperature changes in an organ. This fact makes the interpretation of the records of temperature change quite complicated.

Experimental Technique.—The temperature changes in the organs studied were measured by means of copper-constantan thermocouples combined with mirror galvanometers. The time of vibration of the galvanometers was about seven seconds. The galvanometer deflections were reflected on a common scale, the resistances in each circuit being so adjusted that a deflection of one division on the scale (equal to two millimeters) corresponded to a temperature change of one one-hundredth of a degree Centigrade. The scale covered a temperature range of 6° C. A specially designed potentiometer made possible the immediate introduction into each thermo-

[3] Hill, A. V., *Jour. Physiol.*, 1913, XLVI., 435.

couple circuit of an electromotive force corresponding to a temperature difference of 4° C., so that continuous temperature readings could be made over a range of 14° C.

One junction of each thermocouple was inserted in a constant temperature bath, constant to within one one-hundredth of a degree Centigrade, the other junction being inserted in the organ under investigation. In most measurements one thermocouple was inserted in the brain and one in some other organ or tissue. In some cases, however, three thermocouples were employed.

In order to avoid the influence of bioelectric, or galvanic forces, it is necessary to insulate thoroughly the wires that are inserted in an organ. This was done by enameling the wires and coating them with de Khotinsky cement.

A special metal holder was constructed for the thermocouple that was inserted in the brain. The wires, constantan No. 35 and copper, No. 40, were passed through a hard rubber cylinder, the thermojunction extending about one centimeter beyond the end of the rubber, the exposed portion being covered with de Khotinsky cement which served also to cement the thermojunction in place.

The skull of the rabbit was trephined to make an opening 6 mm. in diameter and the holder clamped in place, the hard rubber rod with the thermocouple junction being then inserted. The depth of penetration of the brain varied in different experiments from 2 mm. to about 8 mm. The trephined opening was made to the right of the mid-line on a level with the posterior superciliary ridge.

The thermocouples inserted in other organs also were constructed of No. 35 constantan and No. 40 copper wire. The wires were soldered together, the constantan wire extending about three inches beyond the junction. By passing this free end through a needle the junction could be readily drawn into the desired position within the tissue.

We wish to express our appreciation of the coöperation of Mr. Seitz of the Electromechanical Engineering Department of the Cleveland Clinic in the construction of the apparatus described above.

The accompanying group of curves shows the effects of various drugs upon the temperature of certain tissues of rabbits, especially of the brain. In a later paper we propose to discuss the relative rôles played in these temperature changes by alterations in the blood circulation, in the blood temperature, and in the metabolism of the organ.

Inhalation anesthesia.—*Ether* in its first stages frequently produced an increase in the temperature of the brain. As the depth of the anesthesia was increased the temperature fell. Fig. 1 shows the

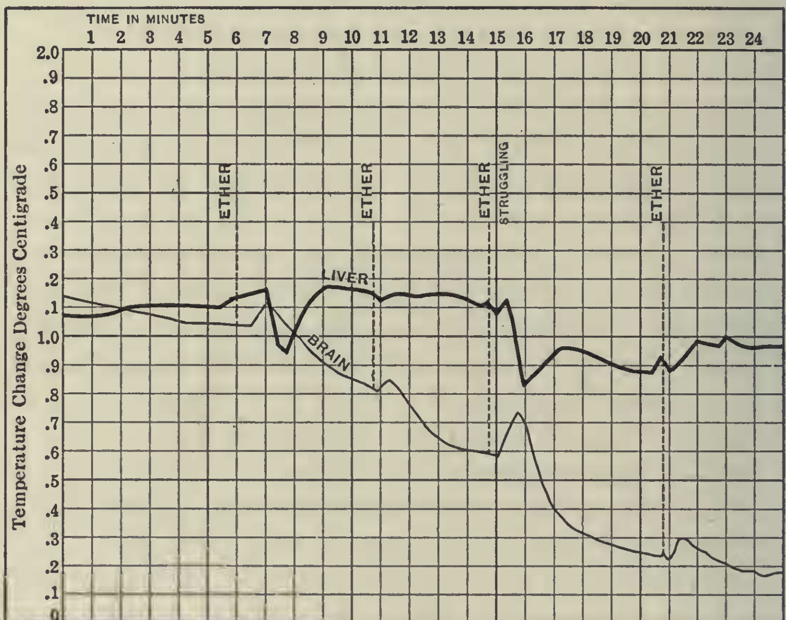


FIG. 1. Effect of the administration of small amounts of ether on the temperature of the brain and of the liver.

effect of the successive administration of small amounts of ether, the intervals being long enough to allow the animal to become nearly conscious between the doses.

Nitrous-oxide as compared with ether showed a less marked change in the temperature and fewer fluctuations, thus giving a more stabilized curve (Fig. 2).

Chloroform showed an initial rise in temperature corresponding to that produced by ether. When full anesthesia was established the temperature fell.

Adrenalin: A number of observations have been made of the effect of the intravenous injection of adrenalin upon the temperature

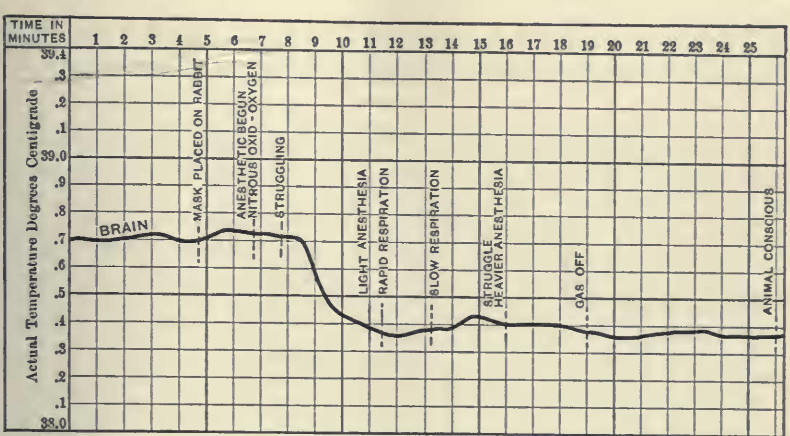


FIG. 2. Effect of prolonged nitrous oxid anesthesia on the temperature of the brain.

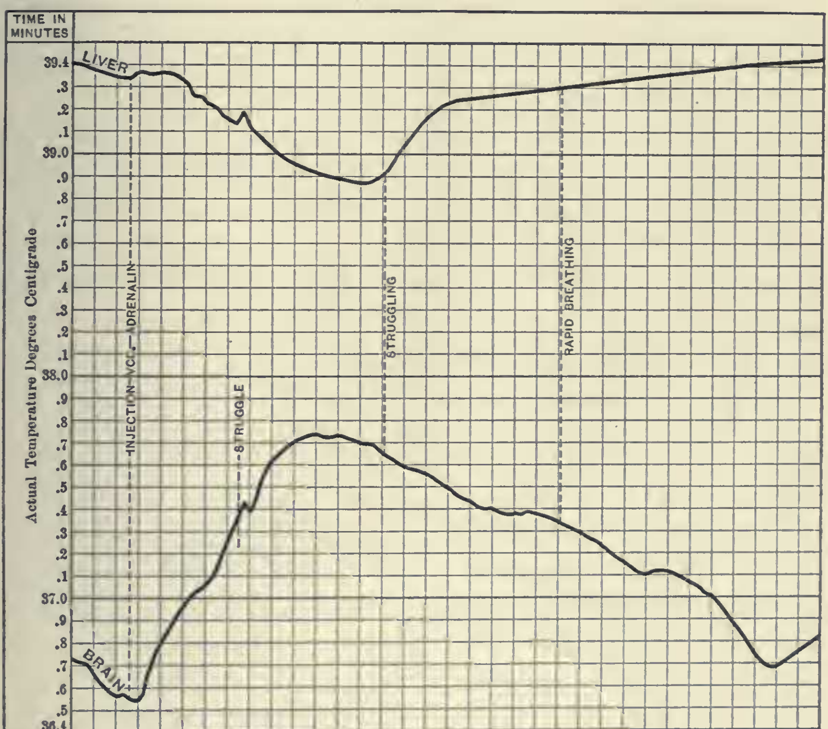


FIG. 3. Effect of the injection of adrenalin upon the temperature of the liver and of the brain.

of the brain, the liver, the thyroid gland, the adrenal glands, the spleen, the intestines, the kidneys, and the muscles (Figs. 3–5).

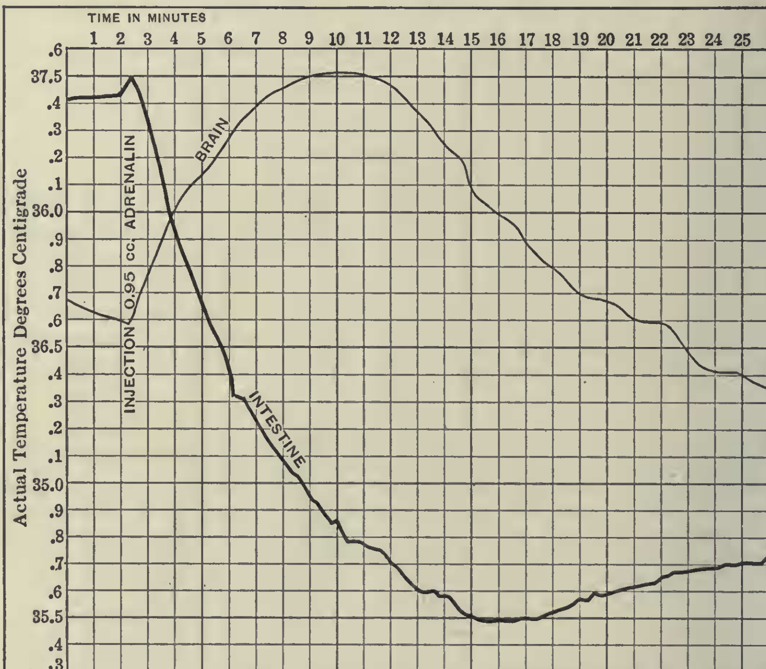


FIG. 4. Effect of the injection of adrenalin upon the temperature of the intestine and of the brain.

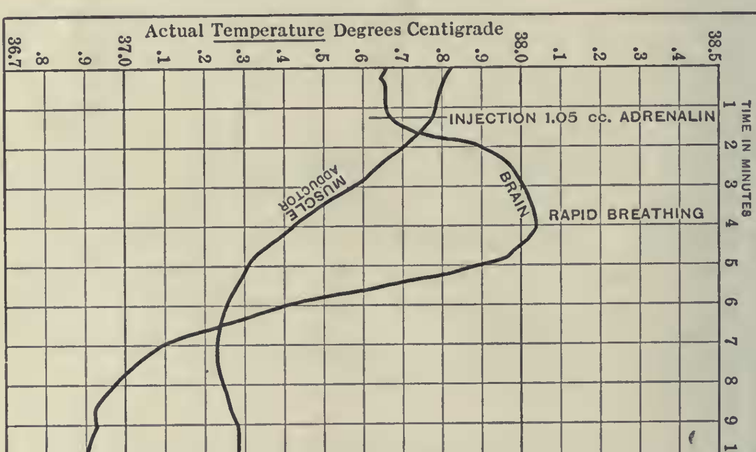


FIG. 5. Effect of the injection of adrenalin upon the temperature of voluntary muscle and of the brain.

The uniform dosage employed throughout was the same as that used in previous researches, viz., 0.4 c.c. per kg. of 1 : 1000 adrenalin chloride (P. D. & Co.).

In every case, the brain showed a very characteristic rise in temperature, the temperature increase continuing for from ten to fifteen minutes and amounting, on an average, to about 0.7° C. The other organs usually show an effect just opposite to that in the brain, the minimum temperature, however, usually occurring a few minutes later than the corresponding maximum for the brain.

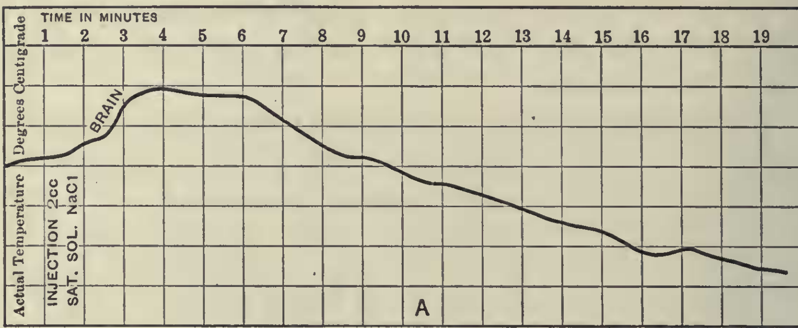
In several cases the temperature of the spleen and of the intestine fell markedly, in some cases as much as two degrees or more (Fig. 4).

In all the above experiments the thermocouple was inserted in the gray matter of the brain and in every case a rise in temperature was noted. It was found, however, that when the thermocouple was placed in the white matter, no change in temperature occurred after the injection of adrenalin.

Amyl Nitrite: The inhalation of amyl nitrite produced a marked rise of 1.1° C. in the brain temperature, the liver showing no decided effect, excepting a slight, continuous decrease in temperature.

Electrolytes: The action of sodium and calcium chlorides has an important theoretical interest. Fig. 6 shows the effects of the injection of these salts upon the temperature of the brain. The well-known antagonistic relation existing between sodium chloride and calcium chloride is strikingly illustrated. The doses given were 2 c.c. of a saturated solution—36 per cent.—of sodium chloride and 1 c.c. of a 10 per cent. solution of calcium chloride.

Sodium Cyanide: The action of a strong poison was shown by various injections of sodium cyanide. The injection of 0.001 *N* solution caused a slight rise of temperature, corresponding to the stage of excitement. The injection of 0.01 *N* solution produced a state of depression, while an injection of 0.1 *N* solution caused an immediate drop in temperature followed by a marked rise; during a period in which violent tremors and convulsions were occurring. During these convulsions the temperature fluctuated over a range of 0.1° C. The result of the injection of still stronger doses was an immediate, rapid decrease in the temperature of the brain followed in a few minutes by death.



ELECTROLYTES

BRAIN: Na Cl (SOLUTION AT 37°C.)

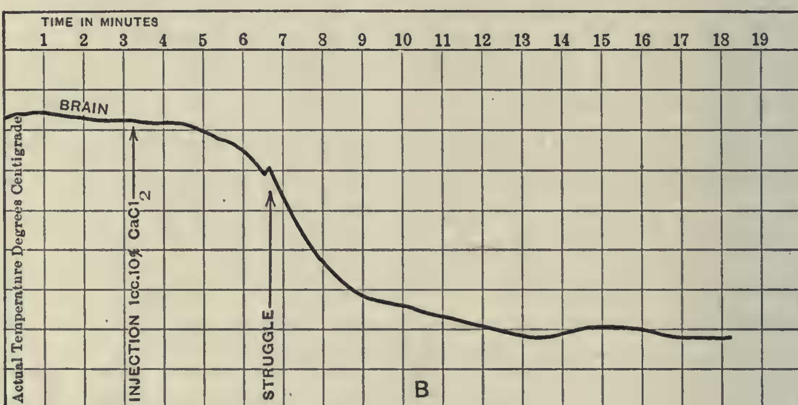


FIG. 6. Effect upon the temperature of the brain of the intravenous injection of (*A*) 2 c.c. of NaCl (saturated—37° C.); (*B*) 1 c.c. of $CaCl_2$ (10 per cent. solution).

SUMMARY.

1. By means of direct measurements of the variations in the temperature of animal tissues, new light may be thrown upon the action of any agent upon the organism.

2. The observations thus far made are consistent with the clinical observations, and with the findings in other forms of physiological research.

3. The opposite effects of the injection of adrenalin upon the brain and upon other organs and tissues demand especial consideration.

4. The use of the biophysical method of measuring variations in function opens the way to further applications of biophysical methods in the study of physiological problems.